

00847, 623

(FILE 'HOME' ENTERED AT 14:51:36 ON 25 JUL 2003)

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:51:45 ON 25 JUL 2003

L1 326 S (DYRBERG, T? OR DYRBERG T?)/AU,IN
L2 50 S (WORSAAE, A? OR WORSAAE A?)/AU,IN
L3 15 S L1 AND L2
L4 7 DUP REM L3 (8 DUPLICATES REMOVED)
L5 361 S L1 OR L2
L6 346 S L5 NOT L3
L7 234 S L6 AND INSULIN?
L8 0 S L7 AND B25
L9 1 S L6 AND (INSULIN?) (3A) (ANALOG?)

FILE 'STNGUIDE' ENTERED AT 14:54:23 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:57:43 ON 25 JUL 2003

L10 8 S (MANDIC, J? OR MANDIC J?)/AU,IN
L11 8 DUP REM L10 (0 DUPLICATES REMOVED)
L12 32 S (B25) (5A) (ASP?)
L13 17 DUP REM L12 (15 DUPLICATES REMOVED)
L14 11 S L13 AND INSULIN?

FILE 'STNGUIDE' ENTERED AT 15:06:45 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 15:08:15 ON 25 JUL 2003

FILE 'STNGUIDE' ENTERED AT 15:09:32 ON 25 JUL 2003

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 15:10:15 ON 25 JUL 2003

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1990:491524 CAPLUS
 DN 113:91524
 TI Identification of residues in the **insulin** molecule important for binding to **insulin**-degrading enzyme
 AU Affholter, Joseph A.; Cascieri, Margaret A.; Bayne, Marvin L.; Brange, Jens; Casaretto, Monika; Roth, Richard A.
 CS Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
 SO Biochemistry (1990), 29(33), 7727-33
 CODEN: BICHAW; ISSN: 0006-2960
 DT Journal
 LA English

=> d 5 ab,

L14 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
 AB **Insulin**-degrading enzyme (IDE) hydrolyzes **insulin** at a limited no. of sites. Although the positions of these cleavages are known, the residues of **insulin** important in its binding to IDE have not been defined. To this end, the binding of a variety of **insulin** analogs to the protease was studied in a solid-phase binding assay using immunoimmobilized IDE. Since IDE binds **insulin** with 600-fold greater affinity than it does **insulin**-like growth factor I (25 nM and .apprx.16,000 nM, resp.), the first set of analogs studied were hybrid mols. of **insulin** and IGF I. IGF I mutants [insB1-17,17-70]IGF I, [Tyr55,Gln56]IGF I, and [Phe23,Phe24,Tyr25]IGF I have been synthesized and share the property of having **insulin**-like amino acids at positions corresponding to primary sites of cleavage of **insulin** by IDE. Whereas the first 2 exhibit affinities for IDE similar to that of wild type IGF I, the [Phe23,Phe24,Tyr25]IGF I analog has a 32-fold greater affinity for the immobilized enzyme. Replacement of Phe-23 by Ser eliminates this increase. Removal of the 8 amino acid D-chain region of IGF I (which has been predicted to interfere with binding to the 23-25 region) results in a 25-fold increase in affinity for IDE, confirming the importance of residues 23-25 in the high-affinity recognition of IDE. A similar role for the corresponding (B24-26) residues of **insulin** is supported by the use of site-directed mutant and semisynthetic **insulin** analogs. **Insulin** mutants [B25-Asp]**insulin** and [B25-His]**insulin** display 16- and 20-fold decreases in IDE affinity vs. wild-type **insulin**. Similar decreases in affinity are obsd. with the C-terminal truncation mutants [B1-24-His25-NH2]**insulin** and [B1-24-Leu25-NH2]**insulin**, but not [B1-24-Trp25-NH2]**insulin** and [B1-24-Tyr25-NH2]**insulin**. The truncated analog with the lowest affinity for IDE ([B1-24-His25-NH2]**insulin**) has one of the highest affinities for the **insulin** receptor. Thus, a region of the **insulin** mol. responsible for its high-affinity interaction with IDE was identified. Although the same region has been implicated in the binding of **insulin** to its receptor, data suggest that the structural determinants required for binding to receptor and IDE differ.

L14 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
 AN 91340787 EMBASE
 DN 1991340787
 TI Receptor binding and tyrosine kinase activation by **insulin**
 analogues with extreme affinities studied in human hepatoma HepG2 cells.
 AU Drejer K.; Kruse V.; Larsen U.D.; Hougaard P.; Bjorn S.; Gammeltoft S.
 CS Novo-Nordisk A/S,DK-2880 Bagsvaerd, Denmark
 SO Diabetes, (1991) 40/11 (1488-1495).
 ISSN: 0012-1797 CODEN: DIAEAZ
 CY United States
 DT Journal; Article
 FS 003 Endocrinology
 037 Drug Literature Index
 LA English
 SL English

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L14 ANSWER 7 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
 TI Receptor binding and tyrosine kinase activation by **insulin**
 analogues with extreme affinities studied in human hepatoma HepG2 cells.
 AB The **insulin**-receptor affinity of five human **insulin**
 analogues with one to four amino acid substitutions was measured with
 human hepatoma cells (HepG2). The binding affinities ranged from 0.05% for
Asp(B25) insulin, 18% for **Asp**
 (B9),Glu(B27) **insulin**, 80% for Asp(B28) **insulin**, and
 327% for Asp(B10) **insulin** to 687% for
 His(A8),His(B4),Glu(B10),His(B27) **insulin** relative to human
insulin. Binding constants obtained by competition experiments at
 steady state with [125I]Tyr(A14)-labeled **insulin** and unlabeled
 analogues and by kinetic studies with [125I]Tyr(A14)-labeled analogues and
insulin gave essentially the same values. The kinetic studies
 showed that differences in affinity between analogues were due to
 differences in both dissociation and association rate constants. The
 affinity for **insulinlike** growth factor I receptor was low,
 ranging from <0.005% for **Asp(B25) insulin** to
 0.6% for His(A8),His(B4),Glu(B10),His(B27) **insulin**. The
 potencies of **insulin** analogues in activation of the tyrosine
 kinase of solubilized and partially purified **insulin** receptors
 from HepG2 cells, measured with the exogenous substrate poly(Glu80-Tyr20),
 ranked in the same order as the binding affinities, the actual values
 being somewhat elevated for the high-affinity analogues, however. We
 conclude that these human **insulin** analogues are active in
insulin-receptor binding and tyrosine kinase stimulation but show
 wide variation in affinity.
 CT Medical Descriptors:
 *hepatoma cell
 *kidney
 article
 controlled study
 human
 human cell
 priority journal
 Drug Descriptors:
 ***insulin** receptor
 ***insulin**: PD, pharmacology
 ***insulin**: CM, drug comparison
 ***insulin** derivative: PD, pharmacology
 ***insulin** derivative: CM, drug comparison
 *protein tyrosine kinase: EC, endogenous compound
 RN (**insulin**) 9004-10-8; (protein tyrosine kinase) 80449-02-1

L14 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:491611 BIOSIS
DN PREV199799790814
TI Metabolically inactive **insulin** analog prevents type I diabetes
in prediabetic NOD mice.
AU Karounos, D. G. (1); Bryson, J. S.; Cohen, D. A.
CS (1) Dep. Intern. Med., Univ. Kentucky Med. Cent., 800 Rose St., Rm. MN520,
Lexington, KY 40536-0084 USA
SO Journal of Clinical Investigation, (1997) Vol. 100, No. 6, pp. 1344-1348.
ISSN: 0021-9738.
DT Article
LA English

=> d 9 ab

L14 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AB The purpose of this study was to determine the relative importance of the
metabolic effects of **insulin** for diabetes prevention by
administering **insulin** or an inactive **insulin** analog by
daily subcutaneous injections to prediabetic mice. A recombinant monomeric
human **insulin** analog, which does not bind to the **insulin**
receptor as a consequence of an alteration of a single amino acid at
position 25 of the B chain, was shown to be equally effective at diabetes
prevention as was intact **insulin**. In contrast to native
insulin, the **insulin** analog did not cause hypoglycemia
after subcutaneous injection. The **insulin** analog, however,
protected young adult mice from diabetes, even when it was initiated after
the onset of extensive lymphocytic infiltration of the islets. Thus,
preventative therapy by daily subcutaneous injections of **insulin**
does not require the hypoglycemic response, or binding to the
insulin receptor to prevent the onset of type I diabetes.

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WEST Search History

DATE: Friday, July 25, 2003

Set Name Query
side by side

Hit Count Set Name
result set

DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR

L13	L12 and insulin\$	7	L13
L12	Worsaae	26	L12
L11	L10 and insulin\$	16	L11
L10	dyrberg	29	L10
L9	L8 and insulin\$	1	L9
L8	Mandic	46	L8
L7	L4 near10 (acid or acidic or hydrophilic)	17	L7
L6	L5 not l1	0	L6
L5	L4 near10 (Asp or aspart\$)	2	L5
L4	(insulin\$)near10(B25)	36	L4
L3	L2 not l1	0	L3
L2	(asp or aspartyl or aspartat\$)near3 (B25)or Asp-B25	2	L2
L1	(insulin\$) and (asp or aspartyl or aspartat\$)near3 (B25)	2	L1

END OF SEARCH HISTORY